Meta-analysis of genome-wide association studies for personality

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Meta-analysis of genome-wide association studies for personality

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Abstract

Personality can be thought of as a set of characteristics that influence people's thoughts, feelings, and behaviour across a variety of settings. Variation in personality is predictive of many outcomes in life, including mental health. Here we report on a meta-analysis of genome-wide association (GWA) data for personality in ten discovery samples (17 375 adults) and five in-silico replication samples (3 294 adults). All participants were of European ancestry. Personality scores for Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness were based on the NEO Five-Factor Inventory. Genotype data were available of ~2.4M Single Nucleotide Polymorphisms (SNPs; directly typed and imputed using HAPMAP data). In the discovery samples, classical association analyses were performed under an additive model followed by meta-analysis using the weighted inverse variance method. Results showed genome-wide significance for Openness to Experience near the *RASA1* gene on 5q14.3 (rs1477268 and rs2032794, $P = 2.8 \times 10^{-8}$ and 3.1×10^{-8}) and for Conscientiousness in the brain-expressed *KATNAL2* gene on 18q21.1 (rs2576037, $P = 4.9 \times 10^{-8}$). We further conducted a gene-based test that confirmed the association of *KATNAL2* to Conscientiousness. In-silico replication did not, however, show significant associations of the top SNPs with Openness and Conscientiousness, although the direction of effect of the *KATNAL2* SNP on Conscientiousness was consistent in all replication samples. Larger scale GWA studies and alternative approaches are required for confirmation of *KATNAL2* as a novel gene affecting Conscientiousness.

Keywords

Personality; Five-Factor Model; Genome-wide association; Meta-analysis; Genetic variants

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The structure of human personality has traditionally been accounted for by a relatively small set of traits. Over the last century, scientific consensus has converged on a taxonomic model of personality traits based on five higher-order dimensions of Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness, known as the Five-Factor Model (FFM).[1] These five dimensions are largely independent and provide a broad description of personality. Neuroticism is commonly defined as emotional instability; it involves the experience of negative emotions such as anxiety, depression, hostility, and the

vulnerability to stress. Extraversion is characterized by positive emotions, gregariousness, and the tendency to be active, seek out stimulation and enjoy the company of others. Openness to Experience involves active imagination, aesthetic attentiveness, variety preference and intellectual curiosity. Agreeableness can be defined as the tendency to be cooperative and compassionate rather than suspicious and antagonistic towards others. Lastly, the dimension of Conscientiousness reflects self-discipline, carefulness, thoroughness, organization, deliberation and achievement.

Personality traits predict a host of social, behavioral and health outcomes, such as job performance, longevity, and many psychiatric disorders, including substance abuse and dependency, mood disorders such as major depressive disorder (MDD), anxiety disorders, and personality disorders.[2-7] For example, Neuroticism reflects a liability trait for MDD and other mood and anxiety disorders and also explains part of the comorbidity among these disorders.[3,6,8,9] MDD is also predicted by low Conscientiousness.[10,11] With regard to substance (ab)use, tobacco smokers score high on Neuroticism and low on Conscientiousness.[12,13] A similar but more extreme pattern is seen for cocaine and heroin users; in contrast, marijuana users score high on Openness to Experience and low on Agreeableness and Conscientiousness.[13] The FFM dimensions further predict tendencies toward different types of personality disorder, with high scores on Neuroticism and low scores on Agreeableness predicting many of the personality disorders and with low or high scores on Extraversion predicting different disorders.[2,14] Personality is also predictive of beneficial outcomes. High Conscientiousness predicts better performance in the workplace[10,13,15] and high Extraversion larger participation in regular leisure time exercise.[16,17]

Twin, adoption and family studies have convincingly shown that each of the FFM personality dimensions is heritable, with heritability estimates ranging between 33% and 65%.[18-21] Lower-order facets that underlie personality dimensions are genetically correlated [22], confirming the notion that the higher-order personality dimensions are to a large extent genetically homogenous. Importantly, genetic influences on personality partly overlap with the genetic factors that influence psychiatric disorders.[3,6,10,20] Thus, gene finding efforts for the major personality dimensions may yield important insights into the genetic etiology of psychiatric disease.

Gene-finding studies for personality, including genome-wide linkage and association studies, have largely focused on Neuroticism, as measured by the Eysenck Personality Questionnaire or as part of the FFM.[23-31] Few studies have also included other traits such as Extraversion.[27,31] The study by Terracciano et al.[31] is to date the only genome-wide association study conducted for all five FFM personality dimensions. This study was performed in an isolated sample of 3 972 Sardinians, analyzing ~362k single nucleotide polymorphisms (SNPs). Although none of the observed signals reached genome-wide significance (lowest p-value 9.4*10-7), several of the top signals were found in genes that are thought to affect behavioral traits and mental disorders through differential brain functioning (for example *SNAP25* for Neuroticism, *CDH13* for Extraversion and *CLOCK* for Agreeableness).

The aim of the current meta-analytic study was to identify novel genetic variants associated with the FFM personality dimensions by combining genome-wide association (GWA) study results from 10 studies, including 17 375 individuals of European ancestry from Europe, the United States and Australia. In-silico replication of the genome-wide significant SNPs was sought in five additional samples consisting of 3 294 individuals.

Materials and Methods

Discovery samples

The samples included in the discovery stage of this study are described below. Approval by local institutional review boards was obtained in all studies and written informed consent was given.

SardiNIA - Italy—The SardiNIA study includes 6 148 related individuals from four towns in the Ogliastra province of Sardinia, Italy.[21] These individuals represent 62% of the population in these towns. Valid NEO-PI-R[1] personality data were available for 5 669 individuals, of which 3 972 were genotyped (56.7% women). The mean age of all participants was 42.8 years (SD=17). The mean age of the men was 43.0 years (SD=18), and of the women 42.4 years (SD=17). The sample has been described in more detail by Terracciano and coauthors.[31]

NTR/NESDA - The Netherlands—The NTR/NESDA study consists of unrelated individuals from Dutch twin families registered at the Netherlands Twin Register (NTR)[32] and participants from the Netherlands Study of Depression and Anxiety (NESDA).[33] Individuals were selected to be genotyped as part of the Genetic Association Information Network (GAIN) initiative[34], of which 1 836 served as controls (mainly from NTR) and 1 862 as cases (mainly from NESDA) in a genome-wide association study for major depressive disorder.[35,36] Controls were selected for absence of an MDD diagnosis and/or a low genetic liability for MDD. In this study, 3 540 individuals (65.6% women) were included with valid NEO personality and GWA data. The mean age of participants was 44.1 years (SD=13). Men were slightly older (M=46.6 years; SD=13) than women (M=42.8 years; SD=13). Personality data from NTR participants were collected in 2004[37] and from NESDA participants between 2004-2007.[33]

ERF – The Netherlands—The Erasmus Rucphen Family (ERF) study is a family-based study including over 3 000 individuals from an isolated population in the South-West region of the Netherlands.[38] There were 2 400 individuals for whom both NEO personality and GWA data were available. The mean age of all participants was 49.3 years (SD=14.9) and women constituted 55.8% of the total sample (M=47.4; SD=15, versus in men M=48.2, SD=14).

SAGE – United States of America—The Study of Addiction: Genetics and Environment (SAGE) is part of the Gene Environment Association Studies initiative (GENEVA) funded by the National Human Genome Research Institute. The sample consists of DSM-IV alcohol dependent cases and non-dependent controls.[39] The original SAGE sample included 4 121 unrelated individuals. Of these, 2 223 subjects had data available from the NEO-FFI. We removed 476 subjects due to non-European ancestry, 8 individuals were removed due to missing genotypes, and 139 were removed because their genotyping consent did not include the use of their personality data. This resulted in a final sample size of 1 600. Of these 1 600, 60.1% were women. The mean age of all participants was 39.6 (SD=9), of the men 40.4 (SD=10) and of the women 39.0 (SD=9).

HBCS - Finland—The Helsinki Birth Cohort Study (HBCS) is composed of 8 760 individuals born between the years 1934-1944 in one of the two main maternity hospitals in Helsinki, Finland. Between 2001 and 2003, a randomly selected sample of 928 males and 1 075 females participated in a clinical follow-up study with a focus on cardiovascular, metabolic and reproductive health, cognitive function and depressive symptoms. In 2004, various psychological phenotypes were assessed, including the NEO personality dimensions.

There were 1 443 subjects with both valid phenotype and genotype data (59.8% women). The mean age of the subjects was 63.4 (SD=3). The mean age of the men was 63.3 (SD=3) and of the women was 63.5 (SD=3). Detailed information on the selection of the HBCS participants and on the study design can be found elsewhere.[40-42]

NAG/IRPG study - Australia—Phenotype data from this study were collected as part of the Nicotine Addiction Genetics study (NAG), for which families were targeted based on heavy smoking index cases identified in previous interviews and questionnaires.[43,44] Personality items, from the NEO-FFI, were included in a questionnaire mailed to all participants. Genotype data came from the Interactive Research Project Grants (IRPG). Valid personality and genotype data were available for 1 349 individuals aged 21-85 years (M=45.4; SD=13.1). Of these, 56% were women (M=45.4, SD=13) and 44% men (M=45.3, SD=13).

QIMR study - Australia—Data from Australian adolescents were collected in twin family studies conducted at the Queensland Institute of Medical Research. Participants were mainly recruited through primary and secondary schools in Queensland for studies of melanocytic naevi (moles).[45] NEO personality data (NEO-PI-R or NEO-FFI) were collected as part of the cognition study (in-person testing, 1996-ongoing)[46], as well as a health and wellbeing study (a mail/phone study 2002-2003)[46], and a study of borderline personality disorder (online/paper survey 2004-2006).[47] For the current study, personality and genotypic data were available for 1 090 individuals (616 females), of whom 254 were monozygotic twin pairs (for whom average phenotypic data were analyzed). Participants ranged in age from 16 to 27 (M=19.4; SD=3). The mean ages in men and women were very similar (M=19.2, SD=3 in men versus M=19.4, SD=3 in women).

LBC1936 – United Kingdom—The Lothian Birth Cohort study consists of a cohort of 1 091 individuals born in 1936 (LBC1936). Most subjects lived independently in the Lothian region (Edinburgh city and surrounding area) of Scotland. The majority of subjects took part in the Scottish Mental Surveys of 1947, and were assessed again on cognition and medical traits at roughly 70 years of age.[48] A fuller description about participant recruitment and testing can be found elsewhere.[48,49] There were 888 subjects (447 female) who successfully filled in the NEO-FFI and survived the DNA and genotyping quality control procedures. The mean age of these 888 subjects was 69.6 (SD=1). The mean ages of the men and women were the same.

BLSA – United States of America—The Baltimore Longitudinal Study of Aging (BLSA) is an ongoing multidisciplinary study of community-dwelling volunteers. Personality traits were assessed from 1989 to 2008, and multiple assessments were available for most participants. Although personality traits are generally stable over time[50,51], to provide more robust estimates, we used the average across all available assessments. For the current study, we examined data from 848 subjects of European descent that were successfully genotyped and completed the NEO-PI-R questionnaire at least once. In this sample, mean age was 68.5 (SD = 17) with 46% of women. The mean age of the men was 60.8 years (SD=16), and of the women 55.9 years (SD=17).

EGPUT - Estonia—The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of University of Tartu (EGPUT). The project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent (www.geenivaramu.ee).[52] In total 38 000 individuals aged 18 years or older participated in this cohort (33% male, 67% female). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians, 3% other).

Subjects were randomly recruited by the general practitioners (GP) and physicians in the hospitals.[53] A Computer Assisted Personal interview (CAPI) was conducted during 1-2 hours at doctors' offices. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. For the current study, GWA was performed on 600 randomly selected subjects with both Illumina HumanCNV370 genotype (array according to Illumina protocol (www.illumina.com) in Estonian Biocenter Genotyping Core Facility) and the NEO-PI-3 questionnaire data available[54]. In this sample the age range was 18-87 (mean 45.7 (SD 16) years). The sample consisted of 250 males (mean age 45.5 (SD=16) years) and 350 females (mean age 45.7 (SD=16) years).

Replication samples

The samples for in-silico replication are described below. In total, the sample size was 3 294 subjects.

NTR+ - The Netherlands—Within the Netherlands Twin Register, several genotyping projects (additional to the first genome-wide genotyping study that was part of the GAIN-MDD study) have been undertaken whose data were combined in the current study to form the replication set. All individuals came from the NTR-Biobank study[55]. In total, 1 920 individuals with valid NEO-FFI and GWA data were available for replication. The mean age of participants was 46.9 years (SD=15) and 67% was female. This sample included 127 MZ twin pairs (254 twins) with phenotype data in both twins. Those twin pairs were treated as one case in the analysis by averaging their phenotypic scores, resulting in a sample with 1 793 subjects for analysis. For 1 475 subjects, GWA data were available on one SNP chip; for 318 subjects, GWA data were assessed on two chips. For the majority of the 1 475 subjects genotyped on one chip (N=1 286; 87%), genotyping was part of the NTR2 genotyping study using the Illumina Human660W-Quad chip. These subjects were unrelated and unselected for any phenotype. The remaining subjects were genotyped as part of the GenomEUtwin study (N=137 subjects; Illumina 370k chip), an Attention Deficit Hyperactivity Disorder study (N=34 subjects; Affymetrix 6.0) and the MDD2000 study (N=18 MDD cases; Illumina 907K chip). Quality control of genotype data and subsequent imputation using IMPUTE software was conducted on separate sets, and on the full set of all genotyped individuals within the NTR. For the purposes of this replication study, after imputation we selected the SNPs from the discovery set that showed genome-wide significance, checked their quality and subsequently analyzed the SNPs.

GERMANY—In this German cohort, 2 420 healthy control participants were randomly selected from the general population of Munich, Germany, and contacted by mail. We included 476 individuals (56% females) with GWA data (Illumina HumanHap300 chip) in this study. Several screenings were conducted before the volunteers were enrolled in the study. First, subjects who responded were initially screened by phone for the absence of neuropsychiatric disorders. Second, detailed medical and psychiatric histories were assessed for the participants and their first-degree relatives by using a semi-structured interview[56]. Third, if no exclusion criteria were fulfilled, they were invited to a comprehensive interview including the SCID to validate the absence of any lifetime psychotic disorder[57]. Additionally, the Family History Assessment Module was conducted to exclude psychotic disorders among their first-degree relatives. A neurological examination was also conducted to exclude subjects with current central nervous system impairment. If participants were older than 60 years, the Mini Mental Status Test was performed to exclude subjects with possible cognitive impairment[58]. Only participants with German descent (all 4 grandparents German) were included. Furthermore, a large battery of personality questionnaires e.g. on

aggression, impulsivity or neuroticism (NEO-PI-R) was obtained as well as data on life events and traumatic events. The mean age of the sample was 46 years (SD=15).

EGPUT2 - Estonia—In the Estonian cohort, additional data of 380 individuals with valid NEO-FFI and GWA data have become available for replication. For a more detailed description of this cohort, see the description above for EGPUT. The mean age of participants was 38.9 years (SD=15). Almost half of the sample (49.5%) was female.

Cilento– Italy—The Cilento study is a population-based study that includes 2 137 individuals from three isolated populations of South Italy. Of these individuals, 859 were genotyped on the 370K SNP map from Illumina. Imputation of 2.5M HapMap SNPs was obtained using MACH software. Genome-wide significant SNPs were selected, checked and analyzed. Data available from the NEO-PI-R questionnaire were available for 343 genotyped subjects representing the final sample. Of this sample, 65.6% were women. The mean age of all participants was 58.9 (SD=19), of the men 59.5 (SD=18.8) and of the women 58.7 (SD= 19).

ERF2- The Netherlands—The ERF2 sample consisted of 302 additionally genotyped individuals with NEO personality data within the family-based ERF study (see the description above for more information on this study). The mean age of these individuals was 50.1 years (SD=14). Women constituted 50.3% of the sample.

Personality assessment

Personality scores for the five factors Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness were based on the 60 items of the NEO Five-Factor Inventory (NEO-FFI) (12 items per factor).[1] Items were answered on a 5-point Likert-type scale ranging from *strongly disagree* (0) to *strongly agree* (4). In the SardiNIA, BSLA, Germany and Cilento studies, these items were taken from the 240-item NEO-PI-R [1]. In the QIMR study, the 60 items were taken from the 240-item NEO-PI-R for part of the sample; the remaining subjects filled in the 60-item NEO-FFI.[1] In the NTR, NESDA, ERF, SAGE, HBCS, NAG/IRPG and LBC1936 studies, personality was assessed using the 60-item NEO-FFI. In the Estonian study samples, the 60 NEO-FFI items [59] were taken from the NEO-PI-3.[54,60]

In each study, summed scores were computed for all five personality dimensions (after reversing negatively keyed items). If more than three items were missing per dimension, the summed score for that dimension was not computed. If three or less items were missing, missing data were imputed by taking the individual's average score for the valid items of that dimension. The mean scores of the five personality dimensions in each study are provided in Table 1.

Genotyping and imputation

DNA was extracted from blood samples in all participating studies. A detailed overview of SNP genotyping, including the platforms used and subsequent quality control, is given in Table 2. The studies used Illumina platforms, except for SardiNIA and NTR/NESDA, which used Affymetrix and Perlegen platforms, respectively. Genotype data were checked in each study independently, using slightly different inclusion criteria. Among the basic checks that were performed were checks for European ancestry, Mendelian errors, gender inconsistencies and high genome-wide homozygosity. Checks for relatedness were carried out in those samples that aimed to use unrelated individuals. Genotype data were further checked based on Hardy-Weinberg Equilibrium (HWE), minor allele frequencies (MAF),

SNP call rate (% of subjects with missing genotypes per SNP) and sample call rate (% of missing SNPs per subject).

In order to compare results at the SNP level, we imputed ~2.5M common SNPs included in HapMap, using the HapMap phase II CEU data as the reference sample. Most studies used NCBI build 36 (UCSC hg18), although in the NTR/NESDA study build 35 (UCSC hg17) was used. Imputation was carried out using IMPUTE for the NTR/NESDA, SAGE and EGP samples (consisting of unrelated individuals).[61] For all other samples, genotype data were imputed using MACH software. For those studies that contained related individuals, a maximum likelihood approach was used that takes advantage of the relatedness among individuals.[62] Throughout this paper, the location of SNPs reported is taken from the build 36 (release 22) HapMap data.

Statistical analyses

GWA analysis in each discovery sample—Genome-wide association analyses were conducted in each study independently using linear regression (under an additive model) and including sex and age as covariates. For those studies that used IMPUTE software to impute missing genotype data, association analyses were conducted in SNPtest, taking the uncertainty of the imputed genotypes into account.[61] For the studies that used MACH to impute their data, either MACH QTL or Merlin was used for association analyses. For the three studies with related individuals (SardiNIA, ERF and QIMR), association analyses were performed in Merlin using a variance components approach, which takes into account the relatedness among individuals in these samples.[62]

Meta-analysis of GWA results across discovery samples—A meta-analysis of the results was conducted using the weighted inverse variance method in METAL (http://www.sph.umich.edu/csg/abecasis/metal/index.html)[63], which computes a pooled effect estimate (*ln*(beta)), its standard error and its p-value by weighing the effect estimates of the individual samples by the inverse of it's variance and by taking into account the direction of effect. Poorly imputed SNPs (r-squared or proper_info < 0.30) and SNPs with low minor allele frequency (MAF<0.01) were excluded, resulting in a final dataset of ~2.4M SNPs. We corrected for any population stratification effects by applying genomic control in each sample prior to meta-analysis. The genomic control inflation factors ($\hat{\lambda}$) for the five personality dimensions for all participating studies ranged between 0.99 and 1.12 (Supplementary Table 1). After applying a genomic control correction to the results from the individual studies, the λ's for the meta-analyzed results were 1.02, 1.01, 1.03, 1.00 and 1.02, respectively, for Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness. The corresponding Quantile-Quantile plots are provided in Supplementary Figure 1. To consider a SNP result genome-wide significant, we used the threshold of $P < 5 \times 10^{-8}$ per trait as proposed for populations of European descent.[64]

Gene-based tests—In addition to the meta-analytic association testing per SNP, we also evaluated the significance of all genes across the genome. We followed the procedure proposed by Liu et al. and incorporated in the program VEGAS[65], which is suitable for meta-analysis results because it does not require raw genotype data but instead uses the p-values of SNPs as input. Gene-based p-values were obtained by using a maximum of 10^7 simulations to correctly account for the linkage disequilibrium (LD) structure among SNPs within a gene. We included SNPs located up to 20kb down- or upstream of a gene. A gene was considered genome-wide significant if a $P < 2.5 \times 10^{-6}$ (0.05 / 20 000) was obtained.

Replication analyses—Replication of the SNPs that turned out genome-wide significant was performed in five independent samples. In each sample, an additive test was conducted,

with sex and age as covariates. SNPs in each sample were checked for minor allele frequency, Hardy-Weinberg equilibrium and if imputed, for imputation quality. The evidence for replication was summarized across samples by conducting a weighted inverse variance meta-analysis. A $P < 0.05$ was taken as significant evidence of replication.

Results

Two SNPs for Openness to Experience on chromosome 5q14.3 and one SNP for Conscientiousness on chromosome 18q21.1 passed the genome-wide significance level of $P < 5 \times 10^{-8}$ in the discovery stage (Table 3). The genome-wide meta-analyzed association results for the five personality dimensions are given in Supplementary Figure 2. Top SNPs for Neuroticism, Extraversion and Agreeableness (Supplementary Tables 2 to 6) did not reach genome-wide significance (lowest P value $> 10^{-8}$).

The two genome-wide significant SNPs for Openness to Experience (rs1477268, rs2032794, r-squared among SNPs ranges between 0.92 and 1 across studies) are located on chromosome 5q14.3 in an intergenic region 135kb downstream from the *RASA1* gene (lowest $P = 2.8 \times 10^{-8}$, with an explained variance of 0.22%) (Figure 1a). The gene-based P value for *RASA1* was 0.02. *RASA1* codes for a GTPase activating protein involved in intracellular signaling and cellular proliferation and differentiation. The gene is highly expressed in the bone marrow and bone, and modestly in the brain.[66] Further, Figure 2a shows that the effect for rs1477268 is in the same direction for nine of the ten studies. Heterogeneity in results across studies was not significant ($\chi^2 = 9.15$, df = 9, P = 0.42). The SNP was genotyped in seven of the studies and imputed with high quality in the SardiNIA, NTRNESDA and ERF studies (r-squared or proper_info > 0.97). The MAFs were very similar across studies and ranged between 0.15 and 0.24. Furthermore, genotype and allele proportions of rs1477268 are in HWE in all studies ($P > 0.01$). The association of these two SNPs with Openness to Experience could not, however, be replicated (combined P across the replication samples 0.53 and 0.55 respectively for rs1477268 and rs2032794, combined P across discovery and replication samples 1.84×10^{-6} and 1.70×10^{-6}).

The genome-wide significant SNP for Conscientiousness (rs2576037) is located in an intron of the *KATNAL2* gene on chromosome 18q21.1 ($P = 4.9 \times 10^{-8}$, explained variance 0.21%.). The second-most significant SNP for Conscientiousness (rs7233515) is a non-synonymous SNP in the same gene (lowest $P = 7.9 \times 10^{-8}$, the r-squared with rs2576037 ranges between 0.92 and 1 across studies, Figure 1b). Variation in this SNP leads to a N88S amino acid change, suggesting a biologically relevant variation. In eight studies the direction of the effect for rs2576037 was the same (Figure 2b). In spite of this, there was nominal significant heterogeneity in the regression coefficients across studies ($\chi^2 = 17.98$, df = 9, P = 0.04). To test which study caused the observed heterogeneity, we reran the meta-analysis multiple times, by each time excluding one of the individual studies. Two studies seemed to account for the heterogeneity. Excluding the Finnish HBCS study (with the largest effect), heterogeneity was no longer significant ($\chi^2 = 11.30$, df = 8, P = 0.19) and the pooled p-value became 4.3×10^{-6}. When excluding the NAG/IRPG study (a small opposite effect), heterogeneity was also no longer observed ($\chi^2 = 11.20$, df = 8, P = 0.19) and the pooled p-value became 2.2×10^{-9}. The SNP was genotyped in seven of the studies and imputed with high quality in the SardiNIA, NTRNESDA and ERF studies (r-squared or proper_info > 0.98). The MAFs were very similar across studies and ranged between 0.37 and 0.46 and distributions were in HWE in all studies ($P > 0.01$).

KATNAL2 encodes a protein similar to the A subunit of the p60 katanin protein and is widely expressed in the central nervous system.[66] Katanin p60 acts to sever microtubules in the axons of neurons and is thought to play a role in neuronal migration, axonal growth and

dendritic pruning.[67-69] Thus, the *KATNAL2* gene may play a role in neurodevelopment. Several other SNPs located in the nearby *PIAS2, HDHD2* and *IER3IP1* genes that are in relatively high LD (r-squared > 0.5) with the top SNP showed suggestive evidence for association ($P < 1 \times 10^{-5}$) (Figure 1b and Supplementary Table 6). The *PIAS2* gene is involved in the regulation of transcription factors involved in the mitogen-activated protein kinase signaling pathway. Less is known about the biological function of the *HDHD2* and *IER3IP1* genes, but all three genes are moderately expressed in the brain.[66]

KATNAL2 was significant in gene-based tests as well (Table 3 and Supplementary Table 7). The cluster of small *TCEB3* genes, located within the *KATNAL2* gene (Figure 1b), was also significant, but the other genes in the region were not genome-wide significant. This suggests that the causal variant may be located in or very near the *KATNAL2* gene rather than in any of the surrounding genes. The association of rs2576037 was again not significant in the replication stage (combined P across replication samples = 0.36), although the direction of effect was consistent with the effect found in the discovery stage (Supplementary Table 8). The combined P value across all discovery and replication samples for rs2576037 was 1.02×10^{-7}.

We also investigated the significance of SNPs that have previously been reported in the first GWA study for the FFM personality traits (Supplementary Table 9) and in the two GWA studies for Neuroticism (Supplementary Table 10).[23,24,30] None of the SNPs reported in these studies were significant (p>0.001).

Discussion

This study suggests evidence for two new loci associated with two dimensions of personality: an intergenic region 135kb downstream from *RASA1* on 5q14.3 for Openness to Experience and the *KATNAL2* gene region on 18q21.1 for Conscientiousness. However, these loci were not unequivocally replicated. The *KATNAL2* gene was also significant in the gene-based test. However, in the replication samples the effect did not reach a level of significance, although there was a consistency of direction of effects Thus, *KATNAL2* might present a novel gene for personality. It should be noted however that even if the signal represents a true finding, the effect size is small. No genome-wide significant results were found for Neuroticism, Extraversion and Agreeableness.

Power analyses showed that the genome-wide significant variants could not have been detected in any of the individual studies at the genome-wide significant level (power to detect these effects at $\alpha=5 \times 10^{-8}$ in sample sizes smaller than 4 000 is less than 1%), but the power to detect these effects in the current meta-analytic study with a sample size of 17 375 is 77% for the top SNP for Openness to Experience and 72% for the top SNP of Conscientiousness. Additional power analyses showed that with a power of 80%, the meta-analysis could detect much smaller effect sizes than any of the individual studies (0.23% explained variance versus 1% to 6.5% explained variance for sample size of individual studies between 600 and 3 972; explained variances correspond to standardized betas of 0.05 versus 0.1 to 0.25).

The findings of the current study show that large-scale collaborative studies with combined sample sizes on the order of thousands or ten thousands still have difficulties in identifying common genetic variants that influence complex phenotypes such as personality traits. It could be that the effects of many SNPs are even smaller than the 0.2% that we were able to detect in this study at a genome-wide significance level. Larger GWA studies may reveal these variants, as has been already successfully demonstrated for human height in a large meta-analytic GWA study of over 180 000 individuals, in which at least 180 loci were

identified together explaining about 10% of the variation in height.[70] In addition, a recent paper using a novel technique to estimate the genetic variance explained by all SNPs, without focusing on genome-wide significance of individual SNPs, showed that common SNP variation explained about half of the heritability of human height.[71] These papers are consistent with the notion that common SNP variation is important in explaining complex highly polygenic traits. It also suggests that the meta-analytic GWA study that we present here was only able to detect the top few SNPs with the largest effect sizes related to personality.

Many other explanations to explain the heritability of complex traits have been put forward.[72] One of these is that other variants that are currently not captured with the genome-wide SNP platforms (including copy number and rare variants) play a role in explaining variation in personality. Next-generation sequencing may reveal more genetic variants that account for the heritability of complex traits including personality. Nevertheless, identification of genetic variants, even if effect sizes are small, remains an important goal, because these variants can be critical entry points to increased understanding of the biological processes underlying personality as well as psychiatric disorders and other personality-related health, social and behavioral outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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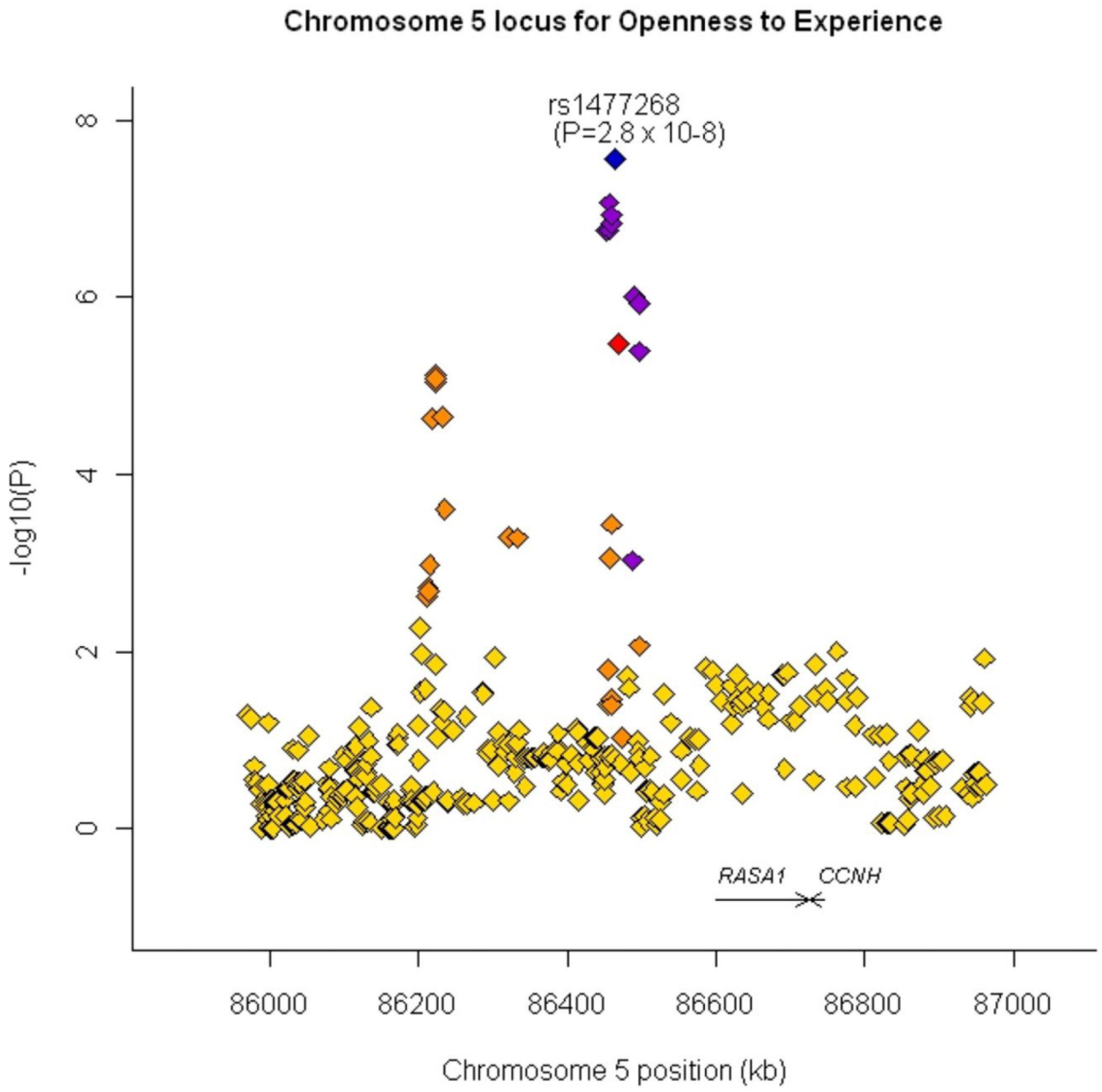


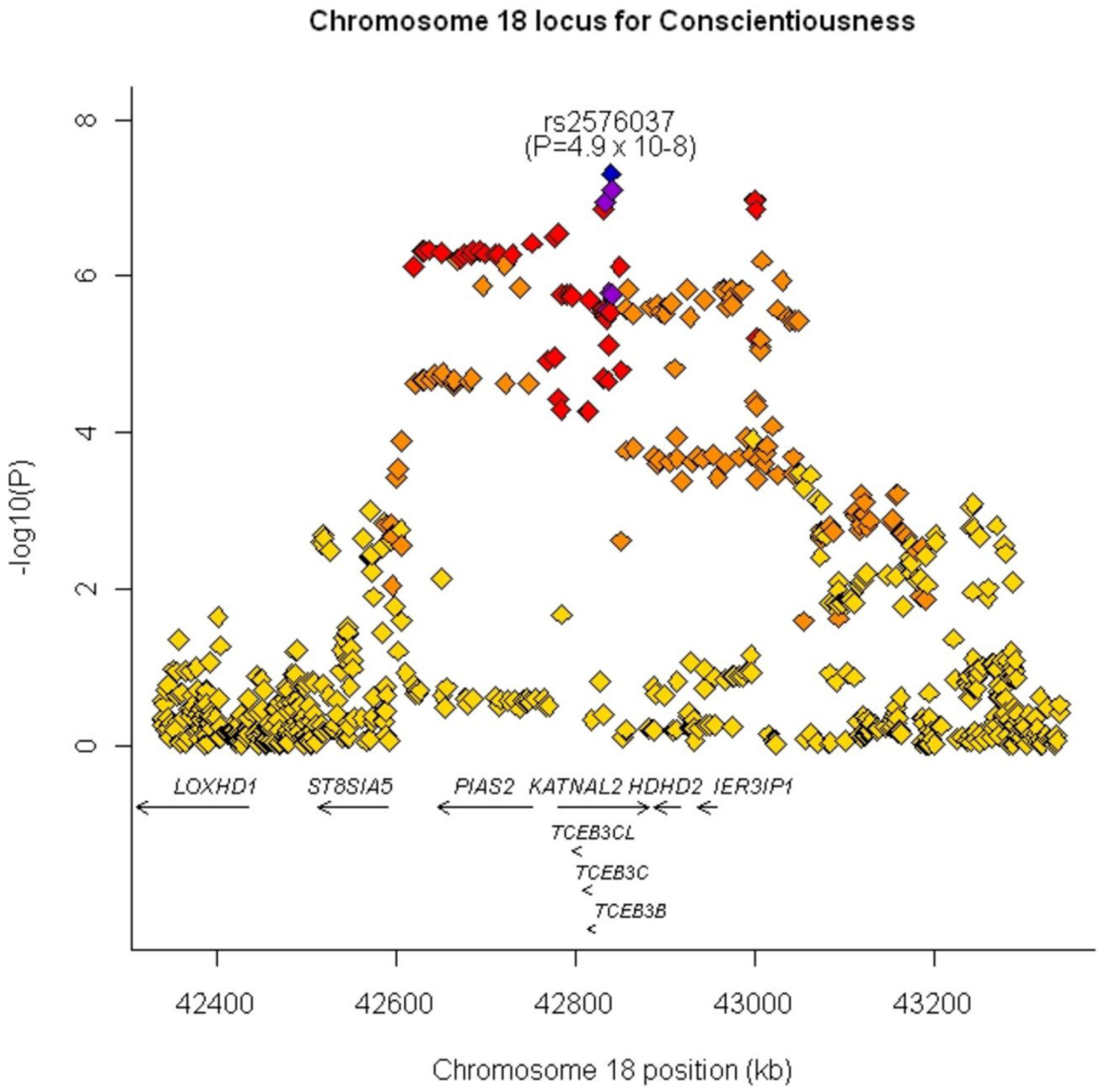


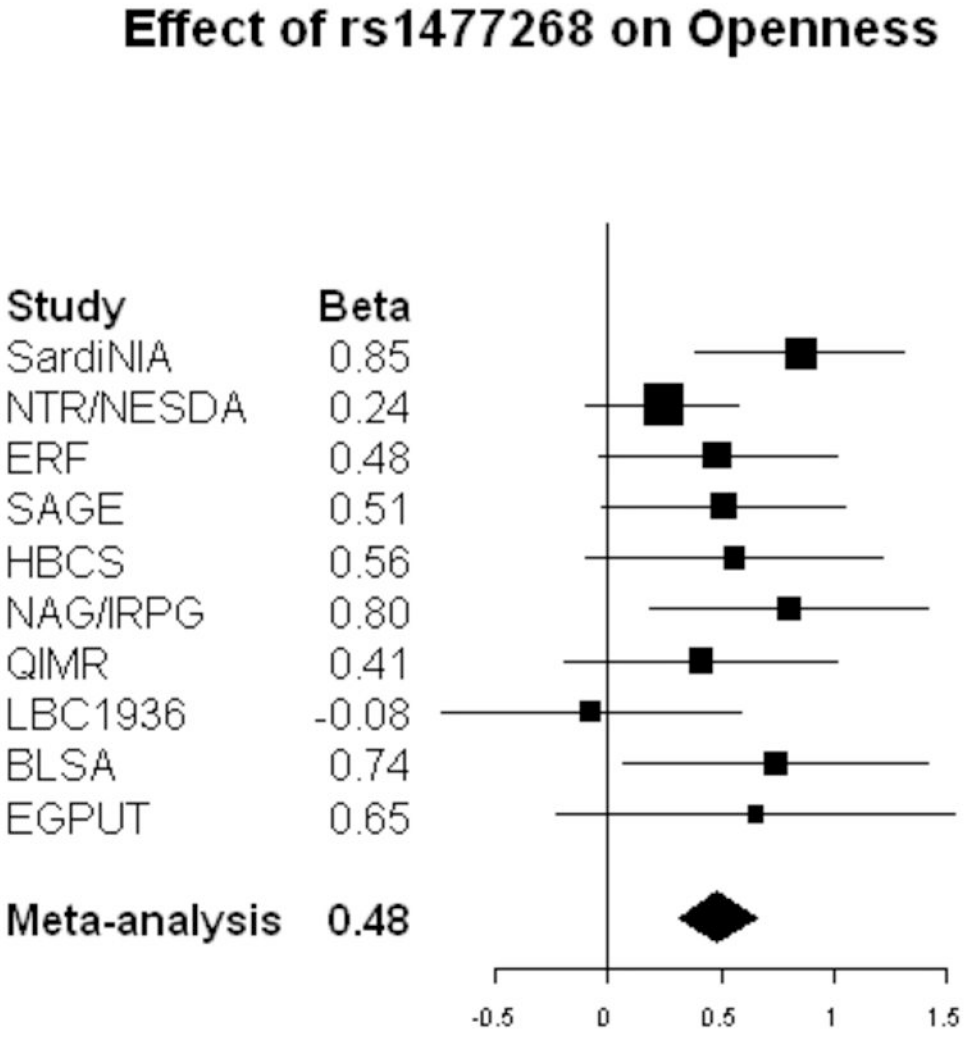
Figure 1.

Regional association plots of the two SNPs genome-wide significant in the discovery set for Openness to Experience and Conscientiousness

a. Chromosome 5 locus for Openness to Experience

b. Chromosome 18 locus for Conscientiousness

Foot note: Physical positions of SNPs and genes are based on build 36 (hg18). The top SNP is shown in blue. SNPs that have an r-squared between 0.8-1 with the top SNP are shown in violet, SNPs with an r-squared between 0.5-0.8 in red, SNPs with an r-squared between 0.2-0.5 in orange, and < 0.2 in yellow.



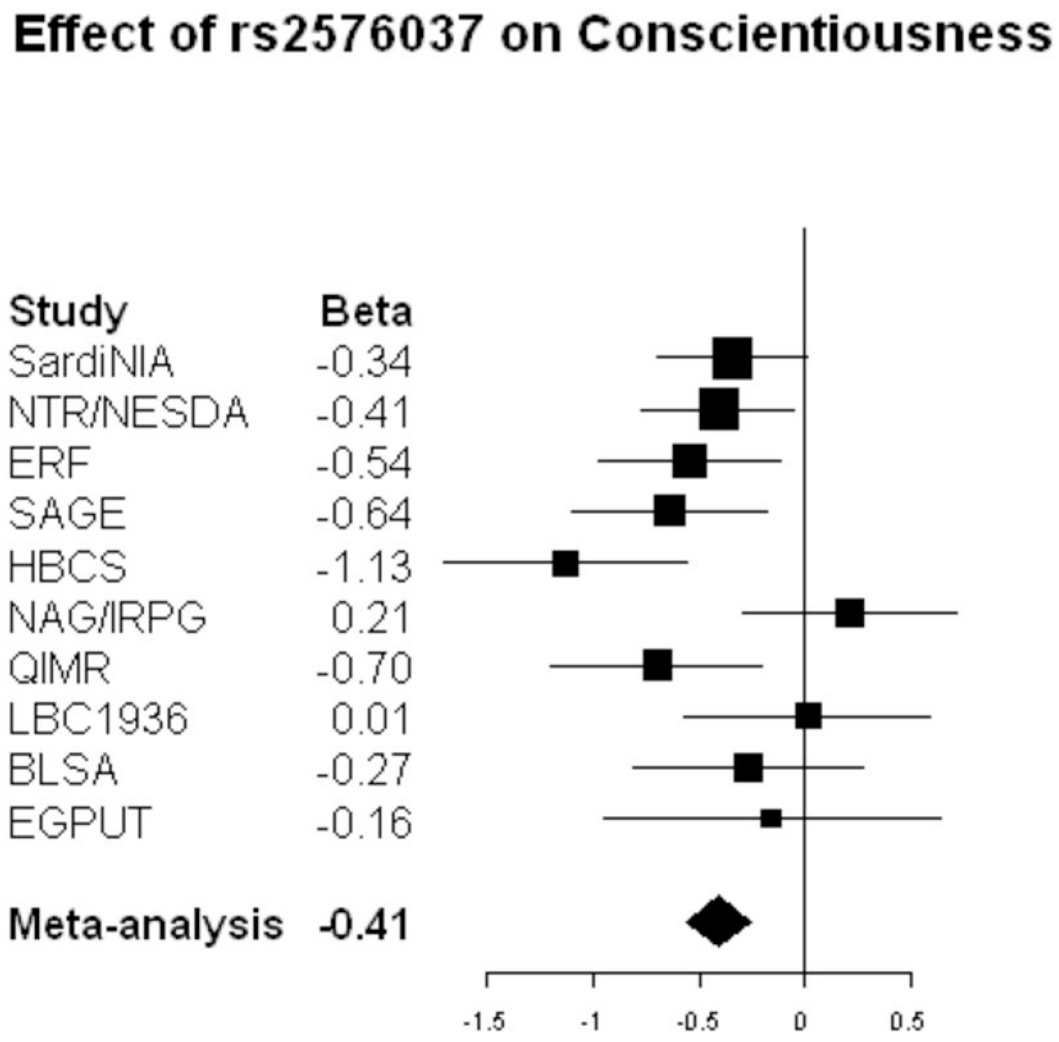


Figure 2.

Association of the two SNPs genome-wide significant in the discovery set with Openness to Experience and Conscientiousness

a. Association of rs1477268 with Openness to Experience

b. Association of rs2576037 with Conscientiousness

Foot note: Effects are reported for the minor allele (see Supplementary Tables 4 and 6).

Table 1

Mean scores of the five personality dimensions in the 10 studies participating in the GWASNEO Consortium, stratified across sex

	Total sample		Men		Women	
Neuroticism	Mean	SD	Mean	SD	Mean	SD
1. SardiNIA	22.6	7.3	20.2	6.5	24.4	7.3
2. NTR/NESDA	21.3	9.6	19.6	9.7	22.2	9.4
3. ERF	19.2	7.9	17.6	7.6	20.5	7.9
4. SAGE	18.9	8.6	18.5	8.8	19.2	8.5
5. HBCS	16.9	9.4	14.5	8.7	18.6	9.5
6. NAG/IRPG	20.0	8.2	18.9	7.8	20.8	8.3
7. QIMR	26.5	6.6	27.0	6.5	26.3	6.7
8. LBC1936	17.1	7.7	15.7	7.5	18.5	7.6
9. BLSA	16.0	6.2	15.3	5.8	16.9	6.6
10. EGPUT	21.9	7.8	20.4	7.4	23.0	8.0
Extraversion	Mean	SD	Mean	SD	Mean	SD
1. SardiNIA	27.9	5.2	27.9	4.8	28.0	5.5
2. NTR/NESDA	26.6	7.4	26.1	7.5	26.8	7.4
3. ERF	28.0	6.5	28.3	6.6	27.7	6.5
4. SAGE	29.3	6.7	28.1	6.6	30.1	6.6
5. HBCS	26.2	7.7	25.9	7.7	26.4	7.6
6. NAG/IRPG	27.7	6.2	27.6	6.1	27.7	6.2
7. QIMR	28.3	5.9	27.4	5.7	29.1	5.8
8. LBC1936	27.0	5.9	26.5	6.1	27.4	5.7
9. BLSA	27.6	5.5	27.2	5.4	28.2	5.6
10. EGPUT	26.2	8.2	25.4	7.8	26.7	8.4
Openness to Experience	Mean	SD	Mean	SD	Mean	SD
1. SardiNIA	26.9	5.6	26.0	5.4	27.6	5.7
2. NTR/NESDA	24.9	5.6	24.7	5.8	25.0	5.5
3. ERF	21.4	5.6	21.2	5.4	21.6	5.8
4. SAGE	27.1	6.1	27.3	6.4	27.0	5.9
5. HBCS	27.5	7.4	26.1	7.5	28.4	7.2
6. NAG/IRPG	26.0	6.2	24.9	6.2	26.9	6.0
7. QIMR	22.5	5.8	21.6	5.9	23.2	5.7
8. LBC1936	26.0	5.8	25.2	5.7	26.8	5.8
9. BLSA	28.4	5.7	27.3	5.6	29.6	5.7
10. EGPUT	22.7	6.7	20.9	6.1	24.0	6.8
Agreeableness	Mean	SD	Mean	SD	Mean	SD
1. SardiNIA	30.7	4.8	29.4	4.6	31.7	4.7
2. NTR/NESDA	32.3	5.2	30.7	5.2	33.2	4.9
3. ERF	31.7	5.6	30.1	5.3	33.1	5.4
4. SAGE	33.2	6.2	30.2	6.3	35.2	5.2

	Total sample		**Men**		**Women**	
5. HBCS	33.0	6.3	31.4	6.3	34.1	6.1
6. NAG/IRPG	32.1	5.5	30.0	5.4	33.7	5.1
7. QIMR	28.3	5.1	27.8	4.7	28.8	5.4
8. LBC1936	33.4	5.3	31.8	5.2	35.0	4.9
9. BLSA	32.4	4.3	31.2	4.0	33.8	4.2
10. EGPUT	27.9	5.5	26.5	5.5	28.9	5.3
Conscientiousness	Mean	SD	Mean	SD	Mean	SD
1. SardiNIA	32.5	5.7	32.6	5.6	32.5	5.8
2. NTR/NESDA	29.3	6.8	29.6	6.9	29.2	6.8
3. ERF	34.5	5.8	34.7	5.7	34.3	5.8
4. SAGE	33.5	6.4	32.3	6.3	34.3	6.4
5. HBCS	34.4	7.6	34.4	7.6	34.5	7.5
6. NAG/IRPG	33.3	6.1	32.3	5.2	34.1	6.0
7. QIMR	29.2	5.6	28.7	5.1	29.6	5.9
8. LBC1936	34.7	6.0	34.4	6.1	34.9	5.9
9. BLSA	32.2	5.6	31.8	5.4	32.7	5.9
10. EGPUT	33.9	6.5	33.2	6.4	34.4	6.5

SD = Standard Deviation

Table 2

Genotyping information in the 10 studies participating in the GWASNEO Consortium

Study sample	Genotyping platform	Quality control of genotyped SNPs prior to imputation			
		HWE p-value	***SNP call rate***	***Sample call rate***	***MAF***
1. SardiNIA	Affymetrix 10K (N=3 329) and 500K (N=1,412) (overlap N=436)	1×10^{-6}	0.90	0.95	0.05
2. NTR/NESDA	Perlegen 600K	-	0.95	0.75	0.01
3. ERF	Illumina 6k, 317k and 370k, Affymetrix 250k	Chip specific	Chip specific	Chip specific	Chip specific
4. SAGE	Illumina 1M	1×10^{-4}	0.95	0.98	0.005
5. HBCS	Illumina 610K	1×10^{-6}	0.95	-	0.01
6. NAG/IRPG	274,604 common SNPs from Illumina 610K/ 370K/ 317K	1×10^{-6}	0.95	0.95	0.01
7. QIMR	Illumina 610K	1×10^{-5}	0.90	0.90	0.01
8. LBC1936	Illumina 61 OK	1×10^{-3}	0.98	0.95	0.01
9. BLSA	Illumina 5 5 OK	1×10^{-4}	0.99	0.97	0.01
10. EGPUT	Illumina 370K	1×10^{-6}	0.98	0.95	0.01

- = no threshold applied

Table 3

Genome-wide significant associations with Openness to Experience and Conscientiousness in the discovery samples of the GWASNEO Consortium for the Five-Factor Model of personality, and associations in the replication samples

					Pooled results in discovery samples			Pooled results in replication samples			Pooled results in all samples
SNP	**Chr**	**Closest gene**	**Location**	**Alleles[a]**	**Effect**	**s.e.**	**P value**	**Effect**	**s.e.**	**P value**	**P value**
Openness to Experience											
rs1477268	5q14.3	*RASA1*	Intergenic	CT	0.48	0.09	2.8×10^{-08}	−0.12	0.19	0.53	1.84×10^{-6}
rs2032794	5q14.3	*RASA1*	Intergenic	CT	0.48	0.09	3.1×10^{-08}	−0.11	0.19	0.55	1.70×10^{-6}
Conscientiousness											
rs2576037	18q21.1	*KATNAL2*	Intron	TC	−0.41	0.07	4.9×10^{-08}	−0.13	0.14	0.36	1.02×10^{-7}

SNP=Single Nucleotide Polymorphism, Chr=Chromosome, Effect = unstandardized regression coefficient, s.e.= standard error, MAF=Minor Allele Frequency, HWE=Hardy-Weinberg equilibrium

[a]First allele is the minor allele, for which the effect is reported.